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Idiopathic epilepsy

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IDIOPATHIC EPILEPSY

- A Review of Some Recent Work -

by

MAURICE AYRES

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INTRODUCTION

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This work was undertaken largely with the view in mind that in my work as a general practitioner I will be continually faced with the problem of treating epilepsy and also the problem of handling a very concerned family who will of course want to know whether or not the patient may marry, why he has the disease and what the outcome is likely to be; who will expect the doctor to be able to discuss the situation with them in an intelligent manner. I felt that I could treat the patient with a reasonable degree of satisfactory results, but as to answering the questions of the family I was in no position to do so, and did not think that I would ever be able to do so unless I understood at least something of the body mechanisms associated with the epileptic state. I have not expected that this thesis should be a profound and exhaustive study of the subject but rather that it should be a brief resume of the high point of the last few years' work on idiopathic epilepsy so that in conjunction with any standard text of neurology I might be better able to deal with the questions of epilepsy and its treatment. As such this article is of value to me. As a research article I would be the first to admit that it is a complete flop, as no one subject is exhaustively treated, nor was it intended to be.

Naturally the first question that arises is just what do I mean by idiopathic epilepsy, and for the purposes of this paper we will say that by idiopathic epilepsy we

mean: the sudden and repeated appearance of seizures, of which convulsive movements or the loss of consciousness or both are the principal elements, without demonstrable lesions, with a typical and demonstrable electro encephalographic pattern. This is a fusion of the definitions of Cobb (16) and Gibbs and Lennox (38). Although one is tempted to use the definition of Gowers who in 1881 gave this definition (40) "Epilepsy is a disease of the gray matter and has no uniform seat, and the cause of the convulsive seizure may be a subtle disturbance in the cellular physiology of the brain rather than a gross lesion", this article will stick to the former. Antell in remarking on Gowers' definition says "the conception of the disease today remains the same" and I am in entire accord with the remark.

I think it would be well before going further to try and correlate some of the terms used in this paper in view of the range of terminology used by the different authors. Genuine, idiopathic, essential or true epilepsy are all intended to be synonymous terms as indicated by these authors, also the terms symptomatic, traumatic, and Jacksonian; and the terms fits, convulsions, seizures, and attacks. For the sake of convenience I will use the initials EEG to stand for the term electro-encephlogram.

Oskar Diethelm (23) very aptly expressed my feeling when he said "Even the clinical study of convulsive disorders

is not yet sufficiently planned. What one ought to look for during a convulsion which one may have a chance to observe and what can possible be investigated before and afterward are known only to a limited extent. There is too much tendency to work along one's own line in interest which usually means a study of the factors of one part of the personality and a neglect of the interrelations". It would appear that rather than attempt to correlate work each man has gone off on his own pet theory and tried to bend all facts to fit into those theories; the result is a surprising lack of surveys covering this field.

I do not feel that any general discussion of epilepsy should be attempted until at least a few words have been said of the EEG in view of the importance which it has assumed in this field in the last few years. The significance of the EEG has been brought to our attention in the literature only in the last 2 to 3 years, but the work with it was started by Berger in about 1929. The articles which made any real attempt at interpretation did not begin to appear until about 1938. The general principle behind the EEG is much like that of the EKG. It measures the potentials as they spread over the brain surface giving patterns which when recorded will give a means of interpreting the physiological processes going on in the brain. The idea intrigues the imagination, but so far its application is limited to the diagnosis of epilepsy and superficial, supra tentorial

brain pathology. As to what these findings are will be described in the body of the paper. It is sufficient here to remark only that it has given us a new and valuable tool for diagnosis, treatment, and possibly prognosis, and should eventually prove of great value in all neurological work.

HISTORY

The history of the convulsive state began in "the dark backward abysm of time" - something of a quarter of a million years ago. At this early date "Empiric thorbibs rushed in (by way of treatment) where angels of modern surgery fear to tread," with the conviction that convulsions were intracranial affairs. This procedure survived among the Gauls but was not followed by the Romans.

Hippocrates maintained that the disease was hereditary - that it affected the phlegmatic rather than the bilious temperament, and that it was due to phlegm in the brain - the fact that it exists in two forms; i.e., idiopathic and symptomatic.

Such historical characters as Galen, Poseidonius, Caelius, and Aurelianus made contributions. The Christian era presented itself with new convictions as pointed out Biblically. The Arabians redressed Greek medicine by merely rearrangement and reappropriation. The coming of the sixteenth century brought medical literature into an expansive field. The Father of the era was Felix Plater (1536 - 1614) who made the first attempt seriously at the classification of spasmodic disorders. With the beginning of the seventeenth century efforts were made to actualize the disease and set forth all complications. Thus has progress been made slowly up to the present time(95).

ASSOCIATED FACTORS

I have spent some time in attempting to separate etiologic and pathologic factors of idiopathic epilepsy but when you consider that the etiologic and pathologic factors of this disease are unknown, an attempt to separate these factors, which may have some bearing on the disease is almost impossible, so instead I am lumping them all together and we will call the combination merely - possibly significant factors in idiopathic epilepsy.

Of all the factors associated with epilepsy probably none is of more general interest than the question of heredity, and as a result we have a mass of statistics that should gladden the heart of any mathematics teacher. The investigators have had a happy time putting their figures together in such a manner that they can interpret and do interpret them as meaning almost anything. Personally I have yet to see a set of figures with which I felt it was possible to make any general statement as to the hereditary factors in epilepsy.

One of the first things naturally in consideration of such a question is - what is the incidence in the general population, so that you can have some basis on which to judge the epileptic group. When I attempted to answer this question I found the following: Cobb (16) in one of his studies had a control group of 250 persons and all their relatives which numbered 1896 and in this group he found an incidence of .025%. He makes the statement that the

general morbidity rate is estimated at .03% in the general population, so that you can judge from that percentage. How or where he found this figure he did not say. Stein (99) in his survey had a control group of 1115 and all their relatives and found an incidence of 1.3%; if you will note this is about 4 times as great as the figures given by Cobb and yet taken in much the same manner. Muskins (69) reports a survey of cases in Hampden county in 1922 and found an incidence of .25% and that the incidence of general population is .07%. That the incidence in France and Switzerland is .3% and Holland .06%, all of which would mean to me only that the incidence in general population is low. I do not believe one is justified in going farther than that in making a definite statement, from this group of figures, and that comparative figures; i.e., those taken under the same circumstances may be of more value.

There have been several rather comprehensive studies of the hereditary factors of epilepsy made but in general they have one big fault as I see it and that is for the most part they have been with or on deteriorated patients entirely, or on non-deteriorated entirely.

The early studies gave several figures. In 1826 Bouchet reported a study showing 3.8% (75); in 1881 Echevirri (24) reported on a group of 136 patients with 553 children and found an incidence of 2.5%. Paskin and Brown (75) made

a study of 162 patients with 342 living children and found an incidence of .29%, which is remarkably low.

Cobb (16) reporting on a study conducted by Lennox and Cobb introduced a new method into the study and so brought it into a new type of figures. For each person studied, the parents, siblings, and children were listed, the total number then being added together and the total number that had suffered from seizures listed. The result was expressed as none per 1000. The results of this study were for a group of 250 normal subjects with 1896 relatives, 2.6 per 1000 suffered from epilepsy whereas in a group of 1,086 epileptic persons (non-traumatic, non-institutionalized) with 9,139 relatives they found an incidence of 21 per 1000. In a group of 234 patients with epilepsy who had suffered head trauma there were only 14 per 1000.

Stein (99) conducted a comparable study using 1000 complete case histories from the Monson State Hospital for epileptics and a control group of 1115 non epileptic individuals. In this group of the epileptic relatives there was an incidence of 3.7% or 37 per 1000 in his control group. You will note that Cobbs' work is all on non-deteriorated patients, and Stein's all on deteriorated patients. Paskind and Brown (73) in their studies between deteriorated and non deteriorated patients show that epilepsy is less prevalent in the children of patients without deterioration than in the children of patients with deterioration.

Cobb and Stein both came to the conclusion after their rather extensive surveys that there was an inherent defect in the germ plasma and as such was transmitted from generation to generation; that direct inheritance was questionable, yet the incidence was too great to consider mere coincidence. Cobb further backed up his theory that the defective germ plasma is transmitted rather than the disease, with the fact that in their study they had included migraine and found that there was a higher incidence of epilepsy among the children of migrainous parents than among the children of epileptic parents. Stein enlarges on the question by stating "this plasma defect gives fertile ground then, for such contributing factors of epilepsy as trauma, infection, birth injury, alcoholism, etc.

From his work with school children in Detroit in 1936, Kimball (54) presents what I feel to be probably the most valuable study with which I came in contact, for in each case there is a definite diagnosis of idiopathic epilepsy and each history was gone into by trained workers. In summarizing this work he says "a simple statement on the part of the parent that no similar attack had ever been experienced by either father or mother was not accepted. It was insisted that at least three generations be reviewed in this respect. In this study the records were completed for over 300 children with the so called idiopathic epilepsy, and a definite familial history was shown to exist in 57% of all cases. In 25% the family history was not known and in only 18% could it be

said with any authority that there was no history of epilepsy in the last three generations.

In attempting to arrive at any conclusion as to the hereditary factor in epilepsy from the foregoing figures, it will be noted that immediately we run into the old story; each had worked up surveys either in a different manner or on different types of groups so that comparison is likely to lead to error rather than to an answer as to its part in the production of epilepsy. So the only answer that I can give the patient who wants to know about the possibility of epileptic children is merely to say that there is a hereditary factor and that the part it plays is not definitely known, but the incidence is too great to consider it mere coincidence.

There is one study that I would like to bring up before we leave the subject of etiology and etiologic factors and that is a study on Migraine and Epilepsy (74):

H.A.Paskind Arch of Neurology and Psychiatry
Relation of Migrain, epilepsy, etc.

		Migraine in family %	Migraine in parent %	Migraine in patient %
1. Nonneurologic group	331	<u>14.4</u>	10.2	3.3
2. Epilepsy	783	35.2	30.8	8.4
3. Manic depressive psychosis	492	34.	26.4	10.
4. Trigeminal Neuralgia	342	37.7	30.1	23.3
5. Psychasthenia	890	25.5	21.7	4.6
6. Dementia praecox	216	32.8	28.7	5.07
7. Tic	136	37.2	37.3	7.6
8. Constitutional inferiority	73	49.3	43.8	5.4
9. Paranoid state	63	23.8	22.2	4.7
<u>a</u> - all known relatives				

The results of the foregoing study would tend to show that while there may be a fairly close relation between migraine and epilepsy it would appear to be more on the basis of germ plasma defect postulated by Stein and Cobb (99)-(16), rather than a closer relation between these over other nervous disorders, for this shows that migraine has just as close a relation to other neuro-psychiatric disorders as it does to epilepsy.

As we enter the long and complicated subject of physico-chemical phenomenon, I think that Pervis-Stewart (90) put very nicely the thought that every author I read, reiterated in some manner, when he said that the epileptic individual appears to possess an "inborn physico-chemical dyscrasia".

Calcium has been the subject of a great deal of work because of its well known relation to convulsion in tetany, where we find a decreased concentration of blood calcium, and a corresponding increase in nerve tissue irritability. Also, it is a well known fact that tissue permeability is affected by calcium and it is postulated that tissue permeability undergoes some change in relation to seizures (57). The fact that the calcium level remains constant during the seizure has been collaborated by many workers, see the reviews of Hirshfelder (48), Griffiths (41) and Scott (85). But Scott and Piggot (85) say a review of the literature on the Ca. content during an epileptic convulsion reveals no adequate series of cases with values based on an accepted method of determination of Ca. content, and come to these conclusions as a result of their findings in 34 cases:

"Hypocalcemia is uncommon in cases with chronic epilepsy and a normal (9-11mgm%) or a hypercalcemia (11-14mgm%) was the usual finding, and there was no change in the level during a convulsion."

There has been some work on Sodium because it has been observed that there is an increase of Sodium in the urine at the time of or shortly after a seizure (34). But the findings of Lennox and Allen (56) and those of Hirshfelder (48) all show that Sodium is a relatively stable element so far as the blood is concerned during a seizure.

Hirshfelder (48) commenting on the observations of Meltzer and Auer of the anti-convulsive properties of Mg. salts and the observations of Dennis and Talbot (22) and Blumgarten (6) who had reported low serum Mg. in a few cases, felt that this might be an etiologic factor and accordingly made an investigation on 79 patients with essential epilepsy at the Minnesota Colony for epileptics. Their findings indicated that: 1, the plasma Mg. is frequently low during the convulsions of essential epilepsy; 2. that the plasma K increased during epileptic convulsions; 3. that the ultrafilterable Mg. is more frequently low and is proportionally lower than the total Mg.; 4. the molar K.-Mg. ratio usually increased during a convulsion especially the ultra filterable portion; 5. all these abnormalities are most intense in the more severe epileptic patients and they tend to return to normal after convulsions; 6. that in the spinal fluid they remain normal. Wolf (105) at about the same time brought

out a study of 100 patients, 33 of whom were essential epileptics and found that the Mg. of the whole blood was below normal in only one case. In view of Greenberg's (42) work that the red blood corpuscles contain more Mg. than does the plasma, Wolf's (105) figures are higher than those that have been obtained by any other worker.

McQuarrie (67) and his collaborators found that the serum K is increased during the convulsion of essential epilepsy and he expressed the belief that there is a leakage of K from the cells, and that this leakage is accompanied by an increased permeability, and is an etiologic factor in the genesis of the convulsion.

Hirshfelder (47), quoting from his own work to show that K salts antagonise the effects of Mg salt more potently than do Ca salts so that an increase in plasma K by antagonizing the anti-convulsive action of the Mg present may play a role in the genesis of convulsions. These aspects should depend on the molar ratio of the K to Mg since the physiologic action is probably exerted by the ions so the molar ratio of unfilterable K-Mg should be the most significant factor.

As they were unable by oral administration of Mg to ameliorate or with KCL to aggravate the epileptic seizure it would seem that this work was something to think about rather than having any practical application at the present time.

Another finding that had attracted much attention was the fact that the epileptic did not have a normal P value. Weil and Leibert (104) made a detailed and comprehensive study of the P in 11 patients, 8 of whom were idiopathic and found that during the convulsion it was true that serum phosphorus as a whole was considerably increased but when this was further broken down, and the non-acid soluble and organic separated they found that the increase was due entirely to the higher value of the non acid soluble phosphorus, while the organic acid soluble remained relatively stable. They also found that it returned to normal on the day following a convulsion so the variability in the phosphorus was considered to be due to the extreme muscular action of the convulsion rather than a cause of the convulsion.

Nathan Rosenthal (88) made complete blood studies of approximately 50 cases and found that in the period between seizures the blood picture was normal. If there was a tendency to polycythemia during convulsions and during ordinary seizures there is often a slight leukocytosis accompanied by lymphocytosis or polyneuclosis. Dr. Patterson (88) found in a study of 300 children that a leukocytosis was constant in over 90% of his cases, using a count of 10,000 as leukocytosis. Very little other work has been done until we find report by Guridham and W. Pettit in 1936 (83) using only 10 epileptic patients and two controls but making extensive counts, they arrived at the conclusion that the white cell count is very variable in epilepsy, confirmed the

finding of a leukocytosis with convulsions but reached the conclusion that it was due in practically all cases to lymphocytes and found very few elevations of eosinophils. Where they found the eosinophils increased, the polys rather than lymphs were increased. One unusual finding was when fits occurred in groups, there was tendency for a low count to be associated with them. They confirmed the finding of Rosenthal (88) that there was an increased eurythrocyte at the time of fits.

With the well-known relation of hypoglycemia to convulsion in diabetes we find that a great many workers have tried in some way to hook this up with epilepsy with very little result. Lennox and his associates (60) finally came to the conclusions that there is no evidence that blood sugar plays more than a passive role in the events associated with seizures for they found that the rise in blood sugar during a seizure is roughly proportional to its severity. The muscular exertion and the emotional concomitants accounting for the increase in blood sugar is confirmed by the work of Hirsch and Haury in 1938(42) and by the work of Pigott 1936(82).

This work has also been approached from the angle of the glucose tolerance curves. Lennox and Belenger (60) after a study of these came to the conclusion that a seizure has not any effect on the shape of a tolerance curve although there is a marked variability in the pre-paroxysmal response.

Goldstein and McFarland (40) feel that any instability of the sugar relating mechanism may well be an expression of the fluctuation in glandular activity, in the tone of the sympathetic system, which can be seen clinically to be disturbed, or in the acid-base balance of the blood. Pollock and Boshes (84) in the study of 90 patients were unable to precipitate convulsion due to hypoglycemia state but they felt that more work should be done on this because of a lack of normals. It will be noted that in the epileptic Gibbs and Lennox (35) found that the epileptic gave abnormal waves at 50mgm % whereas the normal did not until it approached 30 mgm%. Neilson (71) in critizing the work of Lennox and Bellinger (60) felt that their work was inconclusive in that they conducted their tests for only two hours. His work showed the following:

		Fasting	$\frac{1}{2}$ hour	1 hour	2 hours	3 hours	low point
Control	102	88	137	129	103	87	79
Neurotic	30	85	127	123	103	81	77
Epileptic	50	80	119	104	87	76	70

It was found that if the fourth hour had been calculated a still lower point would have been attained, and he feels that this tends to show that the states of hyper insulinism and idiopathic epilepsy merge imperceptively; but he does not feel except in rare cases that the hypoglycemia itself is not sufficient to cause an attack, and that other trauma is necessary to precipitate the attack.

Gibbs and Lennox (35) commenting on the work of

(35)
Lehman say that his work has shown that the same relationship exists between carbon dioxide tension and spontaneous discharges in the peripheral nerve as between carbon dioxide and petit mal seizures. In their work (44) on the variations of the carbon dioxide content which they did by measuring the variations in the internal jugular venous blood and also the carotid artery, they found the Carbon dioxide to be abnormal. When drawn without relation to seizures it was abnormal in 70% of the 94 patients. In the patients subject to petit mal, the carbon dioxide tended to be low whereas in those subject to grand mal, the tension tended to be high. When they had simultaneous grand and petit mal seizures they were preceded by abnormal fluctuations of the carbon-dioxide content in both the arterial and venous blood. The time relation being such as to indicate a causal linkage between the carbon dioxide content of the blood and the seizures these observations are consistent with the EEG evidence that the type of cerebral dysrhythmia present in grand mal seizures is in contrast to that in petit mal attacks, and that carbon dioxide has a pronounced influence on corticle rhythm. They finished their conclusions with the remark that all the available evidence indicates that carbon dioxide plays a significant etiologic role in epilepsy.

It was also of interest to me to note that there must be some relation between dextrose and carbon dioxide

tension for the abnormal waves found in response to a low blood sugar level will respond to changes in the carbon dioxide tension, but if the abnormal waves are not affected by variations in the blood sugar, neither will they be affected by variation in carbon dioxide (58).

There has been some work done on the serum proteins ..Springer (65) determined the serum albumin on 40 patients and found high values averaging 8.3%. Wurth reported an increase in the amount of albumin after seizures (65). Lennox and Cobb found essentially normal values (65). McKenzie found in a large group (65) that the values of albumin and globulin are within normal range and in that of the protein content of the blood drawn immediately after the convulsion though there is a slight increase in serum globulin after the convulsion. Wurth in a study of protein metabolism (41-194) found blood fibrinogen to be the only direct evidence of abnormal protein metabolism.

A finding that has been commented upon by many authors is the unusual number of anatomic abnormalities found in the epileptic. Paskind and Brown (73) made a study of this on 79 deteriorated and 39 non-deteriorated patients for the incidence of somatic anomalies. As the types of these are practically a legion they made no attempt to classify them by type but rather listed the total number for each patient and found that there was a definite increase in the deteriorated as compared with the non-deteriorated patient. They found that some of the more common of these so called stigmata

were: variations in the length of fingers, tubercle at the angle of the jaw, high palate, and anatomical variations in the brain. Along this same line I found that Swift (96) had made a study of the anomalies of the dural sinuses, and found that they are common in idiopathic epilepsy and rare in other diseases. This should be held in mind as a possible etiological factor.

One of the most interesting and unusual pathological descriptions that it has been my privilege to read is Penfield's description of the phenomena event in the human brain during a convulsion. The initial phenomena evident during an attack is the cessation of pulsation in the pial arteries (14); this is unusually widespread over the hemisphere even though the seizures may involve only one part of the body in a local motor or sensory fit. Only occasionally the cessation of cortical pulsation has seemed to be restricted to a local area of the brain. If there is respiratory difficulty the veins become overfull, the venous pressure becomes high and the brain may then bulge, all as secondary phenomena. If there is no respiratory difficulty, the brain does not bulge, there is no venous engorgement, the veins may collapse, and the arteries become gradually blue. At the close of the seizure the arteries begin to pulsate and soon they do more vigorously than before the seizure.

Toward the end of the attack or more often after the cessation of the attack there may occur extraordinary

alteration in the vascularization of the cerebral cortex. There may appear single or multiple constrictions of the large pial arteries obviously capable of arresting the flow of blood through the vessels. On the other hand, there may appear as a sequel to an attack marked flushing of several gyri, so much so that the veins themselves take on an arterial hue. These convulsive sequels occur from the most part in those areas of the brain which have been involved in the production of the epileptic manifestation.

Such vascular sequels appear only in habitual epilepsy. Even after similar electrical stimulation, the cortex of patients who are not subject to epileptic seizures presents no such phenomena. Dr. Lyle Gage's and Dr. Joseph Evans' work in this lab on cats and monkeys, drugs and electric epileptic form convulsions, attained no such response.

These vascular phenomena are a great deal more pronounced in idiopathic or so-called essential epilepsy than in conditions in which an obvious gross lesion exists. It is probably that the cerebral vessels of the patient with idiopathic epilepsy respond more actively than those of the normal person to external stimuli; whether these stimuli are substances in circulation in the blood stream or afferent nervous impulses affecting the brain is not clear.

There have been described lesions of Ammon's horn, described as ischemic changes in the ganglion-cells. Spielmeyer (97) and Winkelman in his summary of work on the Pacchionian bodies (102) did this, yet in view of the

present day findings these again would appear to be the result rather than an etiologic factor in production of seizures. Another anatomical variation which I found interesting, and the information very meager, was a study by Swift (96) in which he makes the statement that anomalies of the dural sinuses are common in idiopathic epilepsy and rare in other disease so should be kept in mind as a possible etiologic factor. As this is essentially due to embryologic defects and birth injury the possibility in relation to heredity, etc. and changes in cerebral flow that is opened by this subject is wide and most certainly is deserving of further investigation.

Commenting on this phenomena, Gibbs and Lennox (36) state this in some cases appeared to be due to stopping of the heart, a rare occurrence in epileptic seizures. One wonders whether in other cases it was due to compression of a cervical artery against the edge of the cranial opening as a result of the increase in intracranial pressure which is always present in a convulsion; yet, from Penfield's (79) observations it would appear that there is little pressure unless you have respiratory difficulty, so it would naturally follow that increased pressure is due not to epilepsy but is the result of epileptic convulsion.

With this phenomena in mind we now have fairly satisfactory proof of the sympathetic control of the cerebral blood flow, for Hessen (18) and Penfield (18) have shown that all the vessels of the brain

down to 40 microns bear vascular nerves and occasional endings which resemble motor end plates; and the work of Ghorobski (11) has shown that after destruction of the sympathetic and parasympathetic there remains yet on the vessels a perivascular nerve plexus. The work of Starraky (100) has demonstrated that they may be made to constrict or dilate by stimulation of different areas of the hypothalamus so showing that there is a central nervous center of control of these vessels even though the efferent pathway is unknown. Forbes (32) has shown that stimulation of the cervical sympathetics causes dilatation and constriction and parasympathetic dilatation of pial vessels. The work of Gibbs and Lennox (36) on the cerebral blood flow becomes of interest for they found no decrease in spinal fluid pressure before an attack which should have occurred if there were any wide spread, sudden, cerebral vaso constriction, preceding a seizure. This was true of both petit and grand mal attacks. They measured the blood flow by a thermo-electric flow recorder in the jugular vein and found no decrease in blood flow preceding an attack but rather a slight rise a few seconds preceding the convulsion. This was also noted by Treadway. All of this would be in keeping with Penfield's observations of the phenomena, and with the knowledge that the caliber of the vessels may be altered by changes in the gaseous content of the blood. Penfield (81) says that even though there does remain the possibility of a spasm

in a single vessel or small variation of the cerebrospinal bed, it would appear that changes in cerebral blood flow were the result of, rather than the etiologic factor in epilepsy.

In regard to the actual pathologic condition of the cells Lennox and Cobb (38) studied 95 specimens and in each case the tissue excised was the starting point for the neuronal discharge which produced focal seizures in the patient in question. They came to the conclusion with their work on the EEG that it is the cells which have been injured and are not yet dead that are the ground in which epilepsy develops, - the so called sick cells. When this is added to the observations of Penfield (79) that a typical seizure may sometimes be produced by stimulation of a questionable area, and that the attacks are produced in general not by stimulating a lesion of the brain but by stimulating the adjacent area of the brain, then consider the histologic study of Penfield, Wilder et al (80) in whose study of 95 specimens from lesions which were the result of traumatic injury, healed abscess of the brain, arterial occlusion and focal ischemia. From a study of these lesions they found that the arteries of a ganglionic scar undergo periodic positive constriction; this may be due to the abnormal scar tissue which surround the vessels or may be due to the abnormal scar tissue which surrounds the vessels or may be that the lack of side branches subjects the arterial trunk to abnormal stretch stimuli. (Stretch seems to be an

adequate stimulus for producing local constriction of cerebral vessels, according to the work of Echlin carried out in our clinic. Such local irritability of the arteries of the central scar would produce the continuing destructive atrophy which is the universal histologic picture characteristic of epileptogenic lesions. In one lesion they found destruction going on 30 years after injury.

They were unable to say that this destruction did not go on in scars which did not give rise to epileptic seizures but only able to point out that there is an extremely slow advancing destruction occurring at the frontier between the lesions and the functional cortex; and that it is in this zone that electrical stimulation may produce in a patient habitual seizures, and it is evident that the scattered occasional vasoconstrictions that occur in the frontier zone produce progressive damage to scattered nerve cells. They summarize their work with this statement "This phenomenon may well be an important mechanism in the charging process that periodically results in the explosive, spreading discharge of ganglion cells, that constitute the physiologic basis of each recurring epileptic seizure".

Hyland (50) quoting from work by Walter makes this statement "Walter has pointed out that a definitely abnormal EEG is found only when the cortex is in some intermediate stage of degeneration and not when it is

completely atrophied.

With the preceding work in mind you are practically forced to the conclusion that the epileptiform seizure is due fundamentally to damaged nerve cells, whether it be idiopathic or so called symptomatic epilepsy. I am fully aware of the fact that this is not an explanation yet of the underlying cause of idiopathic epilepsy for it does not tell how or why we have progressive cell damage in epilepsy. Practically any of the considered etiologic causes of epilepsy might be responsible for cell damage or cell damage might be responsible for practically any of the conditions which have been considered as possible etiologic factors and again we start chasing the egg and the chicken around. But unless we are able to find a constant disturbance which is present in all types of epilepsy, and preceding the actual onset of epileptic convulsions it would appear that these disturbances of metabolism, etc. are the result of central nervous system disturbance rather than the cause of it.

As the brain substance is composed with a high percentage of lipids, it is only natural to assume that any gross disturbance of the brain function as we find in epilepsy should have some relation to these lipids, whether or not they are the underlying causative factor in the production of epilepsy.

McQuarrie and his associates (66) made a study of the blood lipids in epilepsy determining the values of Lecithin, cholesterol and total fatty acids in the blood plasma under various conditions, and found no significant difference in the control group and the epileptic group as to the cholesterol values. The phospholipids showed a greater range of variability in the epileptic group than in the control group. Lecithin was found to be significantly lower and total fatty acids higher than in the non epileptic group. But when they made repeated tests throughout the day they were unable to show any definite and constant relationship between one constituent of the plasma and the attack.

They found also that strongly ketogenic diets which benefitted the epileptic produced a condition of hypercholesteremia and hyperleucithenemia, but that attacks occurred occasionally in spite of the elevation in plasma lipids. The patient with the most severe epilepsy whom they studied had hypocholesteremia as a rule and with attacks there was a marked increase in plasma lecithin, without particular change in the plasma cholesterol.

From the preceding they came to the conclusion that the important relation was between lecithin-cholesterol ratio and the attack rather than the alterations in any one plasma lipid which they had studied.

More recently Cowie and Magee (19) studied various tissues in persons with status epilepticus for lipid content and found the ratio of lecithin to cholesterol to be much higher than that for non-epileptic persons so confirming the work of McQu~~er~~rie and his associates.

Following this on through as to the function of these lipids we find that recent research has indicated that cholesterol and lecithin are essential elements of the cell membranes and in fact are of fundamental importance in determining the semipermeable characteristics of the cell membrane. Cholesterol is thought to diminish the permeability of the cell membrane and lecithin is credited with the opposite effect, and a delicate balance between these two opposite acting lipids is considered to be vital to normal cell function.(2). Some of this antagonism is illustrated by the hemolytic effect of lecithin as opposed to the anti-hemolytic effect of cholesterol and the narcotic effect of cholesterol as opposed to the anti-narcotic effect of the two agents. While lecithin attracts K through membranes (92) cholesterol retards its diffusion. K increases the hygroscopic action of lecithin while cholesterol and Ca retard it (55).

The combination of cholesterol and Ca in high concentration have been shown to produce cellular dehydration and shrinkage. These relationships are probably basic in character and, as expressed in the semipermeability of cell membranes, profoundly influence such functions as water metabolism (10) acid base equilibrium (15), excitation

and conduction in protoplasm and cellular oxidation (2).

Whether or not an abnormality in the cholesterol or lecithin or in the simple ratio between these lipids is an etiologic factor in epilepsy is impossible to say with present knowledge. It is possible that some other factor is the direct cause and that the abnormality of the lipids is merely an associated phenomena. Or again it is conceivable that many factors may disturb the relationship and metabolism of these lipids, which in turn may result in the final necessary conditions for the production of the convulsive state (2).

The many etiologic factors involved in epilepsy and the convulsive state make this latter concept a very plausible one, for it would seem that there should be some one specific factor that is directly responsible for the convulsive state.

(2)
Aird feels that epilepsy is intimately concerned with lecithin cholesterol balance because of the following observation: 1. the increased incidence of convulsive seizures when the relative concentration of cholesterol is known to be diminished, and the diminished incidence of attacks with the relatively higher levels of cholesterol. This he feels is suggested by the variation in the attacks in age (9), season (65), time of day (39), stage of the menstrual cycle (58), pregnancy (89), state of alkalosis or acidosis (15), hydration-dehydration balance (10) and such pathologic conditions as anemia, cachexia, prostration, pneumonia, schizophrenia, cancer and diabetes.

2. Evidence before presented that hypocholesteremia or a high lecithin-cholesterol ratio preceeds and accompanies attacks of epilepsy. 3. The beneficial effects of ketogenic diet and dehydration which have been shown to be associated with an increase in the cholesterol levels of the blood (64). Similarly narcotics (50), at least in part, may be of benefit, because of the relative hypercholesteremia they produce, and from the beneficial reports that have been reported of Kimballs' (54) work with the injection of nerve and brain substance which may likewise have been a result of hypercholesteremia.

(2)

Aird presented his own work on injection of cholesterol into white mice and found that it definitely had anti-convulsant properties seemingly due to the changed permeability of the membrane for convulsive drugs seemed to be more slowly absorbed, and that after the third injection there seemed to be little narcotic effect from the cholesterol.

This ties up very nicely with the modern concept as expressed by Speigel (see introduction) (94), and also with their work for they felt that if epilepsy was due to change in cell membrane permeability then any substance which lowers the density should increase the excitability which they attempted to show by the use of alternating currents of various frequencies. Using some of the most

important of the convulsive agents they got the following results. Anoxemia increases the cellular permeability in the cerebral hemispheres as well as in the subcortical ganglia. Anemia, as produced by ligation of the cerebral arteries gives an initial drop in permeability. (They felt that the later increase was due to coagulation necrosis.) Increased intracranial pressure also usually lowers the conductivity. Increases in the state of hydration (IV injection of distilled water or by artificial alkalosis) increases the permeability and that this effect is still observed even though an increase in intra cranial pressure is prevented by trephining the cranium. Alkalosis causes increased permeability but acidosis has only a slight effect on the membrane. (This perhaps explains the observations in the ketogenic diet that neither acidosis or ketosis alone will have an inhibitory effect on convulsive seizures by Peterman (30). Hyperventilation acts as alkalosis. The anesthetics and hypnotics as ether, chloroform or dial have the opposite effects; that is, they increase the density of the cellular membrane; so, showing at least a direct relationship between cell membrane permeability and excitation of the cell.

Aird (1) in attempting to find the mode of action of the Brilliant Red, as an antoconvulsant, found that in experimental epilepsy it was responsible for a change in permeability of the endothelium of the CNS. That systemic

toxins play at least some part in influencing the convulsive seizure there is no doubt and this observation would merely go to show the probable mode of their action. But to me the important observation in his article was when he quoted the experimental work of Barbour and Able which indicated that the function of the membrane is impaired by injuries to the brain and - quoting Dandy and Elman whose work would indicate that the effect of this persists over a considerable period of time and so not associated with the period of acute injury alone.

Brown and Paskind (7) in referring to the work of Georgi quote him as having come to this conclusion with his work on colloids, after making a study of the blood in persons with epilepsy with reference to the red blood count, sedimentation time, flocculation of plasma proteins and electrical resistance. He concluded: that the underlying mechanism of the epileptic attack is a change in the colloidal character of the nerve cell membrane in response to primary humoral disturbance. Thus the entrance of excitatory factors is permitted.

When we attempt to summarise the etiologic factors in epilepsy, we can say without any hesitation that heredity does play a role; that all of what appear to be physiochemical factors in the production of the convulsive state seem to have some effect on cell membrane permeability. Those which

cause cell excitation seem to cause the cell membrane to become more permeable and vice versa. We also know that cell membrane potential is changed when we have cell damage. From the work with the EEG we know that in epilepsy we have abnormal potentials and rhythms. We know also that in traumatic epilepsy where we can definitely elicit epileptogenic centers, that in these centers we have nerve cells that are damaged. Therefore, it would suggest if not prove that all epilepsy has some organic basis and that petit mal and grand mal are due to variations in pathology.

SYMPTOMATOLOGY

Clark states that but 6% of epileptics show signs of onset and (12) this percentage is upheld by various authors. Therefore the actual symptomatology of the onset of epilepsy becomes a debatable question. That there are definite personality changes before the onset of the fit is no doubt true as summarized by Clark (12). The subject becomes unsocial, quarrelsome, violent and has the inclination to lie. The intelligence remains intact during the development of the character until epileptic psychosis develops with its well known mental failure. Thus would it not seem unfair to classify epileptics into non-deteriorated and deteriorated on the basis of confinement to an institution when intellectual deterioration does not appear until the epileptic psychosis? If so, then our vast accumulation of statistics will not be necessarily accurate. If idiopathic epilepsy does not develop before the age of 21 the chance that it will appear decreases as each year passes (Talbot p. 301). A report from the Craig Colony gave as onset before the age of ten 44.4% and after 20 but 25% (Talbot p.12). This report is confirmed by Lennox and Cobb (18) on 7,350 institutional cases in which the incidence of onset of the disease before the age of 10 was 46% and after 20 but 18% and after age 40, 1.6%. In their study of 804 out patients: 27% before the age of 10, 39% after the age of 20, and 7% after the age of 40 showed signs of onset (8).

Brown studied the onset of epilepsy in 368 non-deteriorated patients and found 25.6% before the age of 10, 39% after the age of 20 and 7% after the age of 40; these also correspond closely with the finding of Lennox(77). In a study conducted by Swift the peak years were found to be the 1st, 3rd, 10th, and 14th years (96).

I have found little work that could be included in symptoms, however, Radeff (87) made an attempt to study 90 deteriorated female patients in regard to temperature variance. He found this so typical that he was able to determine feeble-mindedness or epilepsy from merely looking at the chart. He found temperatures varying from 97 to 101.6. White blood counts were taken on the patients and but 42 were within normal range, 33 were between 11,000 and 16,000, 15 from 15,000 to 20,000 and 6 were 20,000 or more. In view of this fact and considering the conditions of deteriorated epileptics (institutionalized), I venture that both the temperature and white blood counts were inflammatory rather than epileptic in nature. Studies in respiration and pulse were not to be found, although theoretically it would seem that these factors would reflect the epileptic condition, at least to some extent.

The symptoms of the seizures must be divided into two parts, those of Grand Mal seizures and those of Petit Mal. Inasmuch as any standard Neurology discusses in detail these symptoms, it is sufficient for this paper to say that the Grand Mal seizures consist typically of the aura or

warning, which is found in about one-half of the cases, and followed by the tonic stage of which rigidity of the entire musculature is the outstanding feature, usually lasting about 12 minute during which time the patient becomes cyanotic. This is followed by the clonic stage in which the musculature becomes vibratory and undergoes rhythmic contractions. It is during this stage that the tongue is bitten, frothy saliva runs from the mouth, stertorous noise is made. There may be involuntary emptying of the bladder and bowels. Cyanosis diminishes, muscular contractions remain strong to the last jerk, thus ending this stage abruptly. This stage is from 3 to 5 minutes long. Next is the stuporous stage in which the patient lies entirely relaxed, senseless and prostrate for from a few minutes to hours. On waking, the patient has a complete amnesia for the entire period (Talbot p.72).

The Petit Mal or minor epileptic attack may consist of any momentary block of consciousness without impairment of erectness or locomotion or even coordination or muscular actions so long as the actions are automatic. Associated with this momentary loss of consciousness there is always an exaggeration of the tendon reflexes including the plantar and the extensor.(106)

Status epilepticus is only grand mal in which the interval between seizures is too short for recovery (Talbot p.72).

All authors are agreed that an attack may consist of any part of these syndroms, those of petit mal frequently being so fleeting that it is determined only by its regularity of occurrence.

Physical examination will give nothing that is pathognomonic of epilepsy but at the same time a careful physical should be given for use in differential diagnosis. Head scars, scars on the tongue, and injuries for which the patient cannot account should always cause one to check into the history very thoroughly for epilepsy.

The fact that laboratory blood work, while it probably would be within normal limits, would have a tendency to be at the extremes, is shown by a glance at the possible etiologic factors that have been listed in this study.

The hematology as was previously given, if near a convulsion might show almost any type of an abnormality. On the whole, little lab work would be of any significance in epileptic seizures other than for use in differential diagnosis.

The only lab work that would be of real value would be the EEG which will be discussed under diagnosis of epilepsy, and the plasma Lecithin cholesterol ratio in which the Lecithin should be in higher than normal proportion to the cholesterol.

DIAGNOSIS

I found no studies that even attempted to make a statement on whether the incidence of epilepsy was increasing or decreasing nor did I find any studies that attempted to show that occupation had any etiologic connection with epilepsy. Patrick and Levy say that at all ages the differential incidence in males is 60%. Talbot (p.14) has collected a number of authors who have compiled work on this and the table is included.

SEX INCIDENCE OF EPILEPSY

Author Quoted	Percentage	
	Males	Females
Gowers	48	52
Lange	55.9	44.1
Patrick and Levy	62	38
Biswanger	61.9	38.1
Berger	65.0	35.0
Morselli	46.	54.
Spratling	60.1	39.9
Children's Hospital, Boston	55.5	44.6
Massachusetts General Hospital (1914-1926)	56.7	43.3

Gibbs and Lennox (38) found that there were certain types of abnormal wave characteristics; this conclusion was arrived at after several years' work with the EEG and some ninety-four miles of records. They were able therefore to draw conclusions in regard to epilepsy.

Petit Mal was found to be characterized by a wave and spike formation of large voltage repeated three times a second; the individual differences as concerns wave patterns

of course must be taken into consideration.

Grand Mal produced fast waves of high voltage, and again one must account for individual differences in variations; however, these authors noted that the Grand Mal type of activity was unmistakable. If a patient is bordering on a convulsive state the dysrhythmia is present in all records from all points of the accessible cortex. This same type of arrhythmia, although shorter in duration and of less voltage may also be present in patients subject to Grand Mal when there is little or no evidence of seizure, thus revealing psychomotor disturbances.

In addition to these three types of arrhythmias which can be identified with the three well recognized clinical types of seizures, many patients without symptoms show slow waves of large voltage without spikes and square tops. If this is exclusive for persons with present or prospective epilepsy can only be determined by further observation of normal persons as well as those manifesting nervous or mental disorders (non-epileptic). Jasper and Nickols (51) in their sub-clinical work examined a group of behavior problem children. This group was not suspected of epilepsy. EEG examination however, showed the presence of seizure waves. Clinical evidence showed personality deviations and mental conditions often associated with epilepsy. Thus the question, should this be termed epilepsy?

As an index to prognosis Jasper and Nickols deal with the patients as deteriorated and non deteriorated. It was found that a small group of ten non deteriorated patients were free from signs of subclinical epileptic disturbances between attacks. Berger is reported by these authors to the effect that in eleven out of fourteen cases pathologic waves were present; they found that eleven out of twelve psychotic epileptics showed large amplitude slow waves between attacks and all of the thirteen deteriorated epileptics examined showed pathologic waves between attacks. Thus it is strongly suggested that prognosis is possible.

The EEG lends itself to another use-that of determining the possibility of surgical therapy. Jasper and Hawke report three cases in which seizure waves were picked up almost continually over a traumatic scar but not from any other portion of the head. It is to be noted that seizures were not present at the time of examination. The waves picked up were characteristically different from seizure waves, thus suggesting that the form and the localization of the wave are important to surgical intervention. The findings of Lennox and Cobb by clinical criteria were confirmed by Jasper and Hawke by recognizable seizure waves by EEG either during the attack or between attacks.

The diagnostic possibilities of the EEG appears to be widening day by day, but as we find in medicine the swing to the extreme one must question the effect of time upon the test. A note of warning to the over enthusiastic user of the EEG as a diagnostic procedure is sounded by Hyland and

Goodwin (50) "apart from supratentorial cerebral tumor and epilepsy the EEG at its present state of development is of little practical value in the investigation and diagnosis of disease of the brain". Jasper and Nickols (51) make the statement that "localization is of course limited to those portions of the cortex laying subjacent to the head surface, since only indirect gross indications can be obtained of deep lying foci".

The clinical diagnosis of epilepsy would appear to be based on the history of the seizure and the elimination of other conditions. Thus if you have a history of unexplained seizures you have a diagnosis of idiopathic epilepsy. The diagnosis is difficult - in petit mal the seizures may be so fleeting that only after repeated attacks will it be possible to arrive at a diagnosis. In grand mal history one finds such phenomena as injuries about the head from sudden falls, nocturnal pollution, a blood stained pillow, scar on tongue, the history of the cry, incontinence of urine, the post epileptic somnolence, headache, etc.

A finding of considerable interest and possible diagnostic significance is the report in recent literature by Gibbs and Lennox (37) showing the Carbon dioxide tendency in Petit mal to be low and that of Grand mal to be high referred to under etiology.

I shall not attempt to present a differential diagnosis of epilepsy. Cobb enumerates some fifty separate causes of the convulsive state and a discussion of each would necessitate a volume in itself (16); furthermore our

problem is idiopathic epilepsy is to find a causeless convulsive state. A differential diagnosis is also aided by the EEG.

COURSE OF THE DISEASE

The epileptic may become deteriorated or may not deteriorate; he may have convulsions occasionally or he may have them regularly and at frequent intervals; or he may have complete remissions not uncommonly in the course of the disease. We may find him starting out with merely personality changes, finally developing petit mal, then grand mal, and finally even death from status epilepticus or any variation in these possibilities.

The chances of the patient's developing a deteriorated condition according to all authority at the present are rather slight. Paskind (76) studied 304 patients with idiopathic epilepsy from private practice. 32.8% of them had had seizures of from 6 to 10 year duration, 67% of them from 10 to 40 years so he felt that in this group if deterioration was going to develop it should have put in an appearance. In this group he found only 6.5% of the patients showed mental changes characteristic of epileptic deterioration. This work was confirmed by Fetterman (28) and by Barnes (15).

There is a general impression that once a patient is psychotic or deteriorated that he continues to deteriorate. Yet a study by Fetterman and Barnes (5) was made on 105 patients at the epileptic clinic of the Lake Side Hospital Dispensary and they found that the initial examination IQ for the entire group was 74 with a range of from 35 to 130. To date (6 years later) 35 of these patients have been tested

with an interval of a year or more between tests, and each has been tested from 3 to 8 times. Only one patient showed a steady loss and this was very small. Five patients showed consistent gains from one year to another. This differs from the findings of Dawson and Conn (21) who found that there was a uniform decrease in the IQ in epileptic children from the first to the second test.

There is one point in their work that seems to me to be of unusually significant value and that is that on the Babcock test they found that the average efficiency loss was one year. This brings to mind the statement of Vogt (12) that the intelligence usually remains intact during the development of the character so one wonders if the study of the percent of deterioration is of any value for the criteria on which deterioration is based is whether or not the patient is able to hold his job.

At the present time it would appear that we will soon be able to determine by use of the EEG the probabilities of deterioration developing - Jasper and Nickols (51). Also from the EEG we find the answer as to why convulsions are not a criteria of deterioration or an index of how rapidly deterioration will take place. Nickols and Jasper commenting on this factor state "It is not surprising that mental and emotional disturbances should characterise the epileptic personality between fits, when we see the disorganized brain

Waves and momentary subclinical fits revealed in the EEG of patients between overt seizures, and even in some patients who have been free from overt seizures for many years".

Paskind and Brown (73) in a study of the differences between the deteriorated and non-deteriorated found that there were certain differences. The non-deteriorated found the onset of the disease was later, the patients had fewer seizures, and more and longer remissions and neuropathy was less evident in the stock. White in commenting on this makes the statement "The nature of the pathologic change rather than the more conspicuous manifestation, the convulsion is the decisive factor in deterioration", which is amply borne out by the EEG findings. In conclusion all we can say as to the course of the disease is that it will be determined by the pathology and until the exact pathology is found the EEG will be our only guide as to the probable course of the disease.

TREATMENT

In considering the treatment of epilepsy I am going to divide my treatment into several parts, dealing with surgical therapy, sedation, dietary forms of treatment, and a collection of the imperical and non-classifiable treatment. In making this arbitrary classification of treatment, it is for the purpose of convenience only, for as in any other course of therapy actual treatment will consist of a combination, rather than of any one particular type of therapy.

One type of therapy, and something that should be incorporated into all management of the epileptic, is nothing more or less than building the patient up with proper diet and exercise until he is in good physical condition, for the epileptic patient is notorious for his poor physical condition. Talbot (p.83) tells of one patient in his practise that had complete cessation of seizures from mere correction of the body stance, and quotes Lennox and Cobb as having had several other like cases. It is a well known fact that any fatigue, infection, or anything that may affect the general health is harmful, for from the apparent etiologic causes and with the present conception of epilepsy it would appear that one of the underlying conditions is abnormal sensitivity to stimuli.

So far as distinct active therapy goes, I think one thing that has been absolutely neglected in our teaching is emergency treatment, which is nicely outlined by Talbot (p.17) and I think deserves a place in this summary. The

first consideration is to remove the patient as nearly as possible from potential danger, that is, get him away from furniture and hard objects which he might strike during the clonic stage of the convulsion. The clothes should be loosened around the neck and a mouth gag of some kind inserted if possible to prevent biting of the tongue. In status epilepticus hypnotics in large doses are used. I have known of places where the standing order for this condition was 15gr. of sodium amytal intravenously, and I know that $7\frac{1}{2}$ gr. IV frequently will not hold them, so it can be seen that this is a place for heroic measures. In treatment of status epilepticus, where they obtained poor results with ordinary sedatives, Kajdi and Taylor (52) have reported good results from the use of intravenous methylene blue, injecting intravenously 2-20cc of 1% IV. Hot baths, chloroform and morphine have all been used depending on conditions. Talbot also warns against disturbing the sleep which follows, as after effects may be much less if the patient is not disturbed. Another place at which treatment may be instituted is during the aura and so abort the attack. Uscher Parson in 1851 (A 231) said that in cases where the fit commences with a sensation of cold air, creeping along one of the limbs toward the head, apply a string around the limb, and direct the patient to draw it tight when the sensation is first felt, by twisting a stick which is to be worn in the string for that purpose. While I realize that this may sound foolish, it has a good and rational basis, for Lennox and Gibbs (59) found that

anything which the patient must concentrate on mentally will reduce the voltage of waves so making the patient less susceptible to seizures. Talbot also reports during the aura good results from the inhalation of amyl nitrite or mixtures of carbon dioxide if time permits.

All of the preceding may sound like the simple ABC's of symptomatic treatment to the practicing physician, but if you will stop and think back to your first emergency of that type where nurses and attendants were standing at attention waiting for orders and you had to do something in order to save your face even though it might not help the patient, you will realise that something of the type of the preceding discussion would have been a big help. It would have been to me.

Surgical treatment is of little value in idiopathic epilepsy though it has been used empirically by many men for a number of years just in hopes that it might help. Penfield (79) has given a good summary of this and I will merely abstract what I feel are the important points from his article.

With the idea that epilepsy is essentially a disturbance of the sympathetic nervous system, sympathetic gangliectomy has been tried by many surgeons. Penfield in a few instances of well controlled epilepsy in which there was obvious abnormality of the autonomic system in association with the epilepsy, carved out a complete cervical, thoracic

Sympathectomy ganglioneectomy and added to it peri-arterial sympathectomy of both internal carotids and of both vertebrals. In only one instance did the procedure bring undoubted improvement.

Removal of the carotid body and denervation of the carotid sinus is an operation that today is causing in some circles much favorable comment. Penfield says "what ever the nature of the carotid sinus reflex may be cerebral ischemia evidently plays an indispensable role when its activity results in convulsion. Furthermore there is not a tendency among persons with epilepsy to hyperactivity of the carotid sinus, according to Lennox (79) who was unable to produce seizures in 150 epileptics tested by stimulation of the sinus. (Yet the hearsay evidence passing around in circles favorable toward this operation is that 7% of the patients on epileptic wards today are the result of irritable sinuses.) Weiss and Baker (79) concluded that the reflex plays no role of importance in the production of idiopathic epilepsy and that denervation of the sinus should be considered only when specific abnormal hyperactivity of the carotid sinus exists. Marenisco and Kreindler (79) reported that the sensitivity of the carotid sinus is decreased in essential epilepsy and they therefore advised strongly against any further decrease in the activity by surgical intervention. Ask Upmark (79) after an exhaustive analysis of the relation between the carotid sinus and the

and the cerebral circulation advised against the operation.

Subtemporal decompression was recommended early by Kock and has been tried imperically by many surgeons. In rationalising the procedure they pointed out that Lennox measured cerebrospinal fluid pressure in 400 cases (16) and found it to be normal in 71%, low in 8%, and high (200-250) in 17% - which doesn't sound like very rational treatment to the man on the bench. Elsberg and Pike (25) showed that a rise in pressure increased the liability of animals to experimental seizure. Penfield tried it on 14 cases with one cure. He did a simple exploration without following decompression and the result was one cure, so in concluding he says, "in each of the instances of cessation of attack no objective lesion of the brain was found, and it seems likely that both may be examples of the spontaneous arrest which sometimes occurs in essential epilepsy, but rarely if ever with gross lesion of the brain. The results do not justify the procedure in cases of essential epilepsy and should be done only as a final incident in an exploration during which the surgeon has failed to find a removable lesion.

Spinal insufflation of oxygen, an analysis of encephalograph in their clinic has been made by Dr. J.N.Peterson. He found that of 123 persons with epilepsy, who had not any other change in regimen, 10% had remained attack free up to the time of analysis and another 10% stated that they considered their condition improved. On more careful analysis there are

96 patients who were followed for more than a year and 5% of these had remained attack free for an average of 2.8 year. This gratifying result occurred only in young patients under 16 years of age, with attacks of not over 4 years' duration. There were 21 such patients which gave relief from attack for that length of time in 23.8% of that group. This at least suggests that for such patients spinal insufflation is worthy of a trial as a purely therapeutic measure.

I would like to call to your attention the fact that with the use of the electroencephlogram we will probably find the concept of surgical therapy greatly changed in the next few years.

SEDATION

At the present writing this is, along with general physical care, probably the essential treatment of most epileptics in the country - sedation therapy. But it must be remembered that sedation controlling the attacks does not remove the underlying pathological cause and so must be kept up indefinitely . Until the last few years dosage has been largely hit or miss, trial and error methods, - giving it until you had reasonable control of the attacks or until the patients showed toxic symptoms. Perhaps now it will be used a little more rationally. Commenting on this fact Jasper and Nichols (51) state "We have observed a decrease in the amount of epileptiform activity in the EEG of patients not subject to generalized fits following the administration of luminal, sodium bromide, or the use of the ketogenic diet.

The EEG provides a very sensitive check on the effects of such treatment. In some cases it has resulted in the continuation of sustaining doses of luminal when it would otherwise have been withdrawn. In other cases it has suggested the use of anti-convulsive therapy in the treatment of patients who were previously not considered as having epileptoid disorders."

Lennox and Gibbs (59) commenting on use of EEG in sedation say Phenobarbital and Sodium bromide prevent or alter the pathologic activity associated with a seizure, (there is no evidence of localization.) In doses which are not sufficiently large to modify the electrical activity during normal periods, these drugs prevent or modify the electrical activity associated with petit mal seizures. Because the EEG permits recording of the electrical disturbances in the brain which is the epileptic seizure, the technic is an aid not only in the better understanding of epilepsy but in the evaluation of various means of treatment.

On the action of Phenobarbital, Lennox and Gibbs (38) state "This drug appears not only to keep the abnormal disturbances confined to its point of origin, but to disorganize the pathologic rhythm and decrease its amplitude. These are probably merely different aspects of the same basic effect, that is, spread of the abnormal electrical activity is interrupted not only between cortical areas but between cells and probably even between different portions of a

single nerve cell. I would feel that it was logical to assume that other sedatives acted in much the same way, and that they need little further comment, the drugs being used to the point of control of seizures.

If Phenobarbital were particularly harmful when medication is continued over long periods of time, I believe that we would in all probability find more comments in the literature about its toxic effects, though I realise that that is almost impossible in this case to separate the effects of the drug and the possible deterioration of the patient. Observation from the literature would lead to the conclusion that if the writer had something that he wished to substitute for it, then the drug is harmful, if not, he at least minimizes the danger. Let me quote two specific comments that I noted in the literature. Kimball (54) says "Phenobarbital is of limited value in the treatment of epilepsy. The continued use of large doses is detrimental, and does not decrease the severity or frequency of seizures. It is indicated only in special instances and then only for short periods of time". Whereas Barnes and Fetterman (5) in their studies of the mentality of epileptics make this general statement, "It has been the opinion of most authors, that the feeling of security and the apparent reduction in attacks more than offset the possible harm from the use of sedatives". In the light of statements of this type I do not feel that anyone is justified in drawing conclusions as to the value

of sedative therapy until we have data backed up by both clinical findings and those of the EEG showing the effect over a long period of time with an adequate series of cases.

On the use of phenobarbital Cohen and Myerson (17) made an interesting report. In experimenting with different types of therapy they used Benzedrine Sulphate in conjunction with phenobarbital and came to the following conclusions: that this permits the retention of effective doses of phenobarbital that would otherwise be impossible (because the patient would be too stuporous); that it does not increase the number of seizures, instead it appears to exert a beneficial effect in this respect in some cases. It has no effect on blood sugar, NPN, N, or creatinine. When used 5-20 mgm. daily it does not appear to have significant effect on BMR, pulse rate, or blood pressure.

They made one other quite interesting comment, in view of the routine catharsis common on all epileptic wards today and that was that in the treatment of epilepsy when phenobarbital dosage is adequate, there is no necessity for routine catharsis.

In the last few years a new drug has swept the country as the sulfanilimide of epilepsy - Sodium Diphenol Hydantoinate - the results have been good but the toxic effects compared to other forms of therapy also high. Merrit and Putman (86) reporting on this drug came to the following conclusions. They gave the drug to 142 patients (not relieved by other forms of therapy) over periods varying from 2-11 months. Grand mal attacks were relieved in 58% and

decreased in additional 27%. In petit mal it relieved 35% , greatly helped an additional 49%; with psychic equivalent attacks they got relief in 67% and a great decrease in 35%. They had no fatalities but got a toxic demitis in 5% and additional toxic reaction such as tremor, ataxia, dizziness, etc. in 15%. In conclusion they felt that it should be restricted to that group of patients who do not respond to the less toxic forms of therapy. At the end of 2 years and after trying on 350 patients (68), who had not responded to other forms of therapy they found that it had been "more effective" in 79% of the cases and reiterated their conclusions of 1938.

It is of interest to note a fact that almost all common types of sedation are more effective in grand than in petit mal.

DIETARY THERAPY

I have purposely not included water metabolism in a discussion of the etiological causes of epilepsy. The only thing seems to be outstanding is the fact that dehydration seems to give some improvement in the condition of the patient, and that some of the authors were able to precipitate convulsions by use of a positive water balance. Clegg and Thorpe (14) were even willing to go so far that they felt that hydration could be used as a diagnostic procedure in epilepsy. Stone and Cor (98) in a very extensive and detailed study of the water metabolism came to the conclusion that as revealed by

the ratio of fluid intake and output; hematocrite readings and the determinations of blood volume, plasma, volumes, blood halides and body fluid, revealed no significant departure from the normal. Then we find Ziskind (107) after a study with the following observations: blood dilution and water retention were greater in the epileptic than in the non-epileptic. Although extreme amounts of water were a positive factor in precipitating seizures, average amounts did not have this effect. Our findings cast doubt on the efficiency of the dehydration in controlling seizures, and so far as I can determine from reading, this is the present status of the dehydration therapy.

Because of discussion of Mg included in previous section, I will omit any discussion of Mg therapy.

The Ketogenic diet is one of the mainstays of epileptic treatment and as it has now been in use for from 15-20 years we are in a position to begin to judge the effectiveness of the treatment. In a summary of 15 years use of the ketogenic diet at the Mayo clinic, Dr. Helmholtz (45) gives the following: They had 409 cases of idiopathic epilepsy in children under 15 years of age. 31% of the patients who had idiopathic epilepsy were rendered free from attacks and 16% became definitely improved when the Ketogenic diet was given an adequate trial. In all 47% were benefited.

8% of the patients with idiopathic epilepsy whose seizures were controlled by the Ketogenic diet had recurrences of attack within 7 years following the last attack. No

No recurrences occurred after more than 7 years. In discussing the use of phenobarbital in conjunction with the treatment Dr. Helmholz made the statement "with regard to petit mal seizures in particular we have never seen a case where the addition of luminal has been of any benefit".

As to the action of the Ketogenic diet; that is, why it is of value in epilepsy, there seems to be some doubt. A study of this was made by Finkelman and Stephens (30) in which they came to the conclusion that the action was not due to the Ketosis that had been produced. This was confirmed by McQuarrie, (67) who also claimed that Ketosis with acid forming elements did not prevent convulsion. Finkelman quotes Peterman (1925) who said "that acidosis or ketosis alone do not control the convulsions and that only during ketosis and acidosis is there an inhibitory effect on the convulsions. That the shifting of K and intracellular water across the cell membrane may be the mechanism involved in the inhibition of convulsions." It would appear at the present time that the value in the diet lies mainly in its increased concentration of cholesterol (64) as I have previously pointed out.

After Lennox and Gibbs (38) had determined to their satisfaction that in reality the epileptic seizures was set off by partially damaged cells they then set about to try and apply this in some logical manner to therapy. They felt that if there was some way in which they could improve the environment of their so-called "sick" cells, then

they might be able to decrease their irritability. They felt that increasing the dextrose in the blood so that the person would carry a high blood sugar would be a logical means of doing so, and they have tried it on two patients with good results but find that to maintain a high blood sugar is very difficult; they found that dextrose decreased petit mal activity and that sucrose did and the insulin increased petit mal activity. What the results of this will be I do not know, but I do know, as pointed out under carbohydrate metabolism that petit mal but not grand mal is sensitive to both carbondioxide tension and blood sugar levels. Also we know as was before pointed out that Neilsen (71) approximately 90% of the idiopathic epileptics he examined showed periodic or constant low blood sugar during dextrose tolerance tests. So the results of this type of therapy should be very interesting if it is possible to carry it out in any practical manner.

Lennox and Cobb sound a note of caution to any one who tries to use carbon dioxide as a therapeutic measure in petit mal, if the carbondioxide tension is reduced rapidly there is a tendency for the patient to go into a grand mal attack.

IMPERICAL OR UNCLASSIFIED

In any disease, of which as little is known as epilepsy, emperical forms of treatment are legion and deserve some consideration in a paper of this type if only condemnation.

Of course epilepsy could not escape sulfanilimide and surprisingly enough neoprontosile seems to be of definite value in the treatment of the disease; at least Cobb and Cohen (15) gave it to two patients with good results but they happened to take the Ph of the blood at the time the patient was seizure free and found it to be 7.33 and after withdrawal of the drug, and when the patient was again having seizures the Ph was 7.5 so the question of the value of sulfanilamide is very doubtful.

Some work has been done with the vital dyess using Brilliant Vital Red. Cobb and Cohen (15) reported on 10 patients with definite improvement in 7 of them. Osgood and Robinson (72) reported on 13 cases with definite improvement in little over half of them. They felt that it has a greater effect on petit mal than on grand mal. As before mentioned Kadji and Taylor (52) had a seemingly good effect on Status epilepticus with methylene blue. According to the work of Aird on the mode of action of Brilliant Vital Red in epilepsy (1) it would appear that the action is on the endothelium of the central nervous system rendering it more impermeable to convulsive agents. Again we find that more work must be done before we can evaluate this type of therapy but it would seem that there are possibilities.

One of the most interesting studies of therapy that I found was that of Kimball and Gudakunst (54) because of its close tie up with the present conception of epilepsy.

In this work they used 106 cases of idiopathic epilepsy in Detroit school children. They were given daily intramuscular injections of 2cc of a 10% concentration, in liquid form, of lipoids from sheep brain. The results of this were as follows:

Condition	Number	%	Average Number Treatments
Apparently cured	13	12	53
Definitely improved	54	50.9	80
No improvement	39	36.8	90

No barbiturates were given, and they were on a simple well balanced diet. As these were children who were all being kept from school because of epilepsy it means that for the most part they were cases which did not respond to ordinary therapy, so I feel that this form at least deserves more work to have some proper evaluation.

Another thing of interest to me in this study was that these children had 50% fewer convulsions while at school and busy than while at home so again illustrating the observation of Lennox and Cobb (59) that mental activity does influence and depress abnormal waves.

Naturally with the wave of endocrines that have become available in the last few years epilepsy has not escaped. I am not going to try to give summaries of the different work and studies that have been made on this, other than to say that they have been uniformly disappointing. I think the situation is well summarised by Pigott (82) when he says "We see too many epileptics coming into the institution showing gross evidence of dysfunction of the glands of internal secretion to disregard them entirely as an etiological of

concomitant factor and the fact that substitution therapy has failed to relieve the attacks in most of these cases is not sufficient evidence for us to ignore the endocrines but rather a reflection on our ability to determine which gland or glands are at fault, and the inadequacy of the preparations used in treatment."

Another form of therapy that appears interesting is that studied by Antell (4) in which he had treated 6 patients with paratyphoid, typhoid vaccine. All had idiopathic epilepsy; there were 5 children and 1 young adult. In this he caused an elevation of temperature each day for seven days. Results are surprising. Of the children there have been no recurrence of symptoms over a period of 7 months to 2 years. The adult was not benefitted. This deserves further study.

Diathermy has of course been tried. Clegg (13) tried it on 11 cases with uniformly disappointing results but reports Issahyer as reporting favorable results in 75% of 24 cases tested.

Rabies vaccine in isolated instances has been reported through the literature to have some value but studies made by Finkelman et al (31) and by Schipper (91) were uniformly disappointing. But these last three modes of treatment have made me wonder if the reports on the value of fever as referred to by Antell might not have some basis, and be worthy of at least a more careful consideration.

Finkelman (29) tried snake venom in 8 cases of symptomatic all of them were made worse, but Spangler (93) using it on those with seemingly an allergic basis, found some improvement.

Linton (62) suggests the use of amyl nitrite especially where the aura gives warning. He has used it in two cases with good results. I have included this only to show the type of junk that is in our highly scientific magazines, for this report was published as something new in October 1938, yet Talbot gives this as an emergency treatment, routine, of the seizure.

Because of its effect in Migraine, ergotamine tartrate has been tried in idiopathic epilepsy; Loscalzo (63) reporting on this found that it failed to be of any value, and that attacks were increased 45% probably due to withdrawal of sedatives.

Gold and Sodium tetrabromide were tried on 35 cases with favorable results but Epstein (26) oddly enough forgot to tell how much better results he obtained.

It is of interest to note that Diethelm (23) reports that epilepsy is amenable in some degree to hypnosis. This again shows that abnormal waves can be surpassed by mental activity.

To try to draw any particular conclusions from these few high points of treatment is well nigh impossible. One thing that does stand out is the fact that there is being work done and new forms of therapy are being continually

tried so at least the work along this line is not dormant. The most outstanding forms of new therapy that are among the new ones at the present are the Lipoid injection therapy of Kimball, Lennox and Gibbs high blood sugar, the types of dye therapy, and the Sodium diphenol hydantoninate. I have attempted to evaluate each and its present standing. It will be some years before the practical application of each is entirely worked out and their relative value established.

The outstanding thing in the last five years to me is the advent of the EEG, for with it in competent hands we have a means of establishing an early and accurate diagnosis, also a means of following the efficiency of the treatment. From a review of the literature you soon gain the impression that no matter what type of standard therapy is used if early and adequate treatment is given the percent of cures is high, so the next few years should show a definite improvement in the mortality morbidity figures for epilepsy. Another important gain with advent of the EEG is that the danger of over-treatment should be eliminated.

I realize that this should tell the types of therapy that work best in petit mal and those that work best in grand mal but the authors have been delightfully vague on this point and all I can give are impressions. I gained the impression the Grand mal was more susceptible to medication of the sedation type, and petit mal more susceptible to those types of treatment that I have listed as dietary.

SUMMARY

I stated in my introduction that I did not expect this paper to cover the subject of idiopathic epilepsy but rather to cover the newer literature on some of the more important questions that I might be in a better position to deal with the question of epilepsy in general practice. With this in mind I will attempt in a few brief sentences to bring together some of the outstanding points that have appeared in the past few years.

Heredity is apparently a much more important factor in etiology than we had previously considered, although how important is still a question. Migraine is probably not any more closely related to epilepsy than other nervous disorders. Calcium and Phosphorus seemingly have no relation to the disease. It is still a question in my mind as to why we find an increase in sodium in the urine after convulsions. There is a disturbance of Mg. and K of which the K seems to be the important element. It would appear that carbohydrate metabolism is disturbed, and bears some relation to Carbon dioxide. The hematology seems to be of little importance. That numerous anatomical abnormalities seem to be the rule rather than the exception. Lipoid metabolism is definitely disturbed, more especially the lecithin portion. That there is a change in cell membrane permeability but the cause is yet unknown.

In summarizing treatment I think there is little

to be said than I did in my summary at the end of that section - progress is being made.

The EEG should mark the beginning of a new era in this disease for treatment should be improved, and our understanding of the basic process of the nervous physiology should be greatly increased in the next few years.

I feel that with this paper I have accomplished to some degree at least my original purpose which was to get a better understanding of the problems of epilepsy as I will be forced to meet them. If nothing else I feel this paper has done one thing for me and that is that it has given me a basis that I can judge future work on the subject.

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